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Original Article

Changes in salivary cortisol levels in pediatric patients with obstructive sleep apnea syndrome after adenotonsillectomy

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ABSTRACT

Objective: Obstructive sleep apnea syndrome (OSAS) activates the stress response system, including the hypothalamic–pituitary–adrenocortical (HPA) axis. The salivary cortisol, as an index of free circulating cortisol levels, may be used as a measure of HPA axis activity. We examined the change in the salivary cortisol level in pediatric OSAS patients before and after adenotonsillectomy (AT).

Methods: Forty-eight subjects from 80 subjects suspicious of having OSAS were diagnosed with OSAS by overnight PSG, 34 of 48 OSAS patients undergoing AT, and 13 of 34 OSAS patients were finally enrolled prospectively for this study. Before and three months after the AT, the saliva was collected at night before PSG (n-sCor) and in the early morning after PSG (m-sCor) for the measurements of the salivary cortisol level.

Results: Children in the study population ($n = 13$) were divided into mild ($1 \leqslant$ AHI <5, $n = 5$), moderate ($5 \leqslant$ AHI <10, $n = 3$), and severe (AHI $\geqslant 10$, $n = 5$) OSAS groups. The mean preoperative AHI in the children was 14.7, and the mean postoperative AHI was 0.33. The percentage of children with AHI <1 after AT was 92.3%. Postoperative m-sCor, the difference of cortisol level (sub-sCor: m-sCor minus n-sCor), and the ratio of cortisol level (r-sCor: m-sCor/n-sCor) showed significant difference postoperatively.

Conclusions: AT was associated with improvements in PSG and subjective symptoms in pediatric OSAS patients. In addition, these improvements were significantly related to normalization of salivary cortisol level after AT. Although further study on salivary cortisol levels needs to be done, the measurement of salivary cortisol level before and after AT may predict the outcome of AT as a treatment of OSAS.

1. Introduction

Pediatric obstructive sleep apnea syndrome (OSAS) is one of the most frequently diagnosed sleep disorders. Pediatric OSAS has been reported to occur in 1–3% of all children, with potential adverse effects on cognition, school performance, and the cardiovascular system, as well as economic consequences [1–7]. Abnormal breathing patterns of OSAS range from reduced airflow (flow limitation, hypopnea) to repeated cessation of airflow (apnea) with increased respiratory effort, which may cause hypoxic stress on the body.

Such chronic hypoxic stress due to OSAS may activate and influence body stress response systems, such as the autonomic nervous system and the hypothalamic–adrenal–pituitary (HPA) axis [8]. A previous study showed that catecholamine concentrations – an indicator of sympathetic nervous system activity – were elevated in OSAS patients [9].

In a recent study [10], we demonstrated that the ratio of post- to presleep salivary cortisol (the cortisol slope, rCor) was negatively associated with OSAS severity, which might reflect a chronically stressed HPA axis and suggest the usefulness of salivary cortisol as an indicator of chronic stress in OSAS in the pediatric population.

Total serum cortisol contains both free (physiologically active) and protein-bound (physiologically inactive) cortisol; however, salivary cortisol is strongly correlated with active serum free cortisol [11]. Salivary cortisol also displays a characteristic circadian

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rhythm similar to that of serum cortisol, with a nadir at night and a peak level just after awakening.

Adenotonsillar hypertrophy is the most commonly identified risk factor for pediatric OSAS. Thus, adenotonsillectomy (AT) is the treatment of choice for pediatric OSAS patients who have enlarged tonsils and adenoids [1,2]. Many doctors have been dependent on physical findings and sleep history reported by parents to diagnose OSAS in the pediatric population. As a result, post-AT results may also have been evaluated by parents' reports and relief from symptoms such as snoring.

However, Gozal et al. [12] reported that although age and body mass index *z*-score were the two major factors affecting the post-AT apnea–hypopnea index (AHI), asthma and the magnitude of pre-AT AHI contributed modestly to post-AT AHI among non-obese children. Thus, it is important to understand the severity of OSAS in children prior to AT, which will help in predicting and treating residual OSAS in high-risk children.

Polysomnography (PSG) remains the gold standard test for diagnosing sleep-disordered breathing (SDB) in both adults and children, although other diagnostic tools have been tried to diagnose SDB in children [13–16]. However, it is not easy to routinely perform PSG in all children with a suspicion of SDB because it is time-consuming and costly. It may be even harder to perform PSG after treatment for OSAS in children.

Thus, given that PSG is not likely to be performed in all children with a suspicion of OSAS or in those who have undergone treatment for OSAS, other diagnostic methods may be needed, even if they are not as precise as PSG, to assist in finding the high-risk group of children before treatment and to re-evaluate children after treatment to assess any residual OSAS.

At this point, the measurement of salivary proteins, especially in children with a suspicion of OSAS, may be practical; it is a safe, easy, non-invasive, and rapid method that is especially suitable for children.

Recently, Malakasioti et al. [17] reported that children with moderate to severe obstructive sleep apnea and a hypertrophic tonsil phenotype showed reduced morning serum cortisol levels, and Park et al. [10] reported that the ratio of pre-PSG to post-PSG salivary cortisol levels showed a consistent negative relationship with OSAS severity in children. Based on these results showing a relationship between cortisol levels and OSAS severity in children, we aimed in this study to evaluate changes in salivary cortisol before and after AT and to assess the utility of salivary cortisol levels as an index of postoperative results.

2. Methods

2.1. Subjects

Thirteen children aged 3–11 years who had enlarged tonsils/adenoids and were diagnosed with OSAS by overnight PSG were enrolled prospectively in this study; all patients attended the Department of Otolaryngology, Head and Neck Surgery, St Vincent's Hospital, Suwon, Republic of Korea, between July 2011 and February 2013. The patients who underwent AT completed postoperative PSG about three months after the AT.

After history-taking from the children's parents, all children underwent a complete otolaryngological examination, and the parents of each child completed two sleep questionnaires before and after AT: Korean versions of the modified Pediatric Epworth Sleepiness Scale (KMPESS) and the Obstructive Sleep Apnea-18 survey (KOSA-18).

Based on parental history and otolaryngological/physical examinations, all 13 children were confirmed to have no antrochoanal polyps, nasal polyposis, congenital craniofacial abnormalities, neuromuscular dystrophies, prior history of cardiac or airway surgery, history of cardiomyopathy, or pneumopathy.

Full, attended overnight PSG was performed, and saliva from each child was collected with specialized tubes around 22:00 before PSG and then the next morning after PSG (within 30 min after awakening). At three months after AT, a full attended overnight PSG and salivary collection before and after PSG were again performed.

We explained the study procedures to all participants and their parents, and informed consent was obtained from the parents before enrollment. The study protocol was reviewed and approved by the Ethics Committee for Clinical Studies at St Vincent's Hospital, The Catholic University of Korea.

2.2. Questionnaires

The same questionnaires were used as in our previous study [10]: the KOSA-18 survey to evaluate the quality of sleep and the KMPESS to assess daytime sleepiness.

KMPESS was modified from ESS for adults, in that 'without alcohol' was deleted and 'as a passenger for a few minutes' was substituted by 'in a car'. Both were administered before and after AT.

2.3. Polysomnography

Standard overnight multichannel PSG (Somnologica software and Embla S700/A10 hardware, Embla Systems, Broomfield, CO, USA) was performed for all participants before and at about three months after AT. The PSG parameters were as follows: four electroencephalogram channels, bilateral oculograms (ROC, LOC), one ECG lead, three electromyograms (chin, right and left anterior tibialis muscles), and a body position sensor.

The respiratory state was evaluated with a nasal pressure transducer and an oral–nasal airflow thermistor, and respiratory effort was evaluated with thoracic and abdominal respiratory effort sensors (piezo type). Peripheral oxygen saturation (SpO_2) was assessed by pulse oximetry. Snoring was measured using a neck vibration sensor or by recording nasal pressure. All measures were scored initially by a certified technician and then reviewed by a doctor. The AHI was defined as the number of obstructive apnea and hypopnea events per hour. The diagnostic criterion for OSA in pediatric subjects was AHI >1 event/h. Obstructive apnea was defined as the absence of, or >90% reduction in, airflow for >90% of the entire event with continued chest wall and abdominal movement, which lasted for at least two regular breaths, compared with the previous baseline amplitude. Obstructive hypopnea was defined as a $\geqslant$50% reduction in air flow for >90% of the entire event, which lasted for at least two regular breaths, with a decrease in SpO_2 of $\geqslant$3% or electroencephalogram arousal (compared with the previous baseline amplitude).

2.4. Measurement of salivary cortisol

The same measures were used as described in our previous study [10]. Briefly, according to the manufacturer's protocol, saliva sampling was avoided within 60 min after eating a major meal, and patients were educated not to eat or drink dairy products or sugary foods and to brush their teeth before sampling on the day of the PSG test. The child's mouth was rinsed with water 10 min before saliva sampling.

Sampling was performed in special tubes around 22:00 before PSG and around 07:00 the next morning after PSG (within 30 min of waking). Whole saliva was collected, refrigerated within 30 min, and then frozen at or below −20 °C within 4 h after collection. On the day of the assay, samples were thawed completely, vortexed, and centrifuged (1500*g*, 15 min). All samples were

assayed in duplicate for salivary cortisol using a sensitive enzyme immunoassay (Salimetrics, State College, PA, USA) as an in vitro diagnostic measure of adrenal function. The salivary cortisol ratio was defined as the ratio of the measurements after PSG to those before PSG (r-sCor), and the salivary cortisol subtraction was calculated by subtracting the measurements before PSG from those after (sub-sCor).

2.5. Statistics

All analyses were conducted using SPSS software (SPSS, Inc., Chicago, IL, USA). To assess the normality of the data, the Shapiro–Wilk test was used. Fisher's exact test or paired *t*-test (two-tailed) was used to evaluate the changes of salivary cortisol values, and PSG parameters between pre- and postoperative states. $P < 0.05$ was considered statistically significant.

3. Results

In total, 80 children aged 3–11 years with suspected OSAS and adenotonsillar hypertrophy were enrolled prospectively. Of these, 48 subjects were diagnosed with OSAS by overnight PSG, and 34 of the 48 underwent AT. Nineteen of the 34 OSAS patients who underwent AT completed the postoperative PSG at about three months after AT; of these, six subjects were excluded for inadequate sampling or sampling errors. Thus, 13 patients were finally analyzed. Demographic and PSG findings are presented in Table 1. The subjects ($n = 13$) were subdivided into mild ($n = 5$, $1 \leqslant$ AHI <5), moderate ($n = 3$, $5 \leqslant$ AHI <10), and severe ($n = 5$, AHI $\geqslant 10$) OSAS groups. The mean preoperative AHI in the children was 14.74 ± 14.13, and the mean postoperative AHI was 0.33 ± 0.48 episodes per hour.

The percentage of children with normalized PSG parameters after AT was 88.2%. Postoperative PSG parameters in terms of snoring time, arousal index, flow limitation, AHI according to sleep stage (REM index and NREM index), and oxygen desaturation index were improved significantly compared with those in the preoperative PSG.

The quality of life (QoL) score in KOSA-18 decreased from 69.92 ± 24.82 preoperatively to 35.00 ± 11.39 postoperatively, showing a statistically significant improvement ($P = 0.001$), demonstrating that AT could improve the QoL in OSAS children. There was also significant change in the KMPESS score between pre- and postoperative assessments. The KMPESS score was 6.77 ± 5.80 preoperatively and 2.46 ± 1.98 postoperatively ($P = 0.016$).

As shown in Table 2 and Fig. 1, salivary cortisol levels were measured at night before PSG (n-sCor) and in the morning after PSG (m-sCor). The postoperative m-sCor was significantly higher than the preoperative m-sCor ($P = 0.031$), but n-sCor showed no significant change. Significant changes were also found in r-sCor and sub-sCor values, with the r-sCor and sub-sCor postoperative levels being significantly higher than the respective preoperative levels ($P = 0.009$ and 0.013, respectively).

Table 1
Demographic, polysomnographic, and questionnaire data.

	Preoperative ($n = 13$)	Postoperative ($n = 13$)	*P*-value
Gender			
Male	11 (84.6%)		
Female	2 (15.4%)		
Age (years)	6.5 ± 2.6		
BMI (kg/m^2)	17.1 ± 3.3		
AHI	14.74 ± 14.13	0.33 ± 0.48	0.003
$0 \leqslant$ AHI $\leqslant 1$	0	12 (92.3%)	<0.0001[a]
1< AHI <5	5 (38.5%)	1 (7.7)	
$5 \leqslant$ AHI <10	3 (23.0%)	0	
$10 \leqslant$ AHI	5 (38.5%)	0	
REM-AHI	29.26 ± 32.79	0.79 ± 1.33	0.008
NREM-AHI	11.58 ± 11.56	0.19 ± 0.37	0.004
ODI	7.55 ± 12.10	0.12 ± 0.31	0.046
Lowest SaO_2	88.46 ± 9.60	91.69 ± 5.96	0.317
KMPESS	6.77 ± 5.80	2.46 ± 1.98	0.016
KOSA-18	69.92 ± 24.82	35.00 ± 11.39	0.001

BMI, body mass index; AHI, apnea hyponea idex; REM-AHI, AHI during AHI during REM sleep; NREM AHI, AHI during NREM sleep; ODI, oxygen desaturation index; SaO_2, arterial oxygen saturation; KMPESS, the score in the Korean version of modified pediatric Epworth Sleepiness Scale; KOSA-18, the score in the Korean version of OSA-18.
Median (interquartile range) tested by Wilcoxon rank-sum test.
[a] *P*-value tested by Fisher's exact test.

4. Discussion

Both plasma and salivary cortisol levels, useful indices of HPA activity, show characteristic circadian variations, peaking in the early morning, declining throughout the day, and reaching a nadir during late evening or the early sleep state [18]. Although the cortisol level in saliva is lower than that in blood because total serum cortisol contains both physiologically active cortisol and a physiologically inactive protein-bound cortisol fractions, salivary cortisol is strongly correlated with free serum cortisol [19]. Moreover, salivary cortisol is more closely correlated with serum adrenocorticotropin than is total serum cortisol, and it may therefore reflect the secretory activity of the HPA axis more accurately [11].

Although the HPA axis is suppressed during early nocturnal slow wave sleep, it may be activated by sleep deprivation and fragmentation. Nocturnal awakening is associated with pulsatile cortisol release and autonomic activation. Buckley and Schatzberg [18] suggested that there may be significant interplay of HPA axis hyperactivity with untreated OSA and upper airway resistance syndrome. They hypothesized that OSA may cause activation of the HPA axis through a mechanism of autonomic activation, awakening, and arousal.

However, we demonstrated that salivary cortisol levels among a pediatric control and OSAS subgroups were significantly different and, in particular, that the salivary cortisol slope (r-sCor) between n-sCor and m-sCor was flattened in the group with moderate to severe OSA [10].

Our previous results seem to be consistent with many previous reports: for example, (i) Malakasioti's recent article [17]; (ii) the cortisol slope (ratio of post- to presleep cortisol) could reflect daily cortisol rhythm and show statistically significant changes (slope flattening) in stressful situations [20,21]; (iii) Miller et al.'s review; and (iv) Heim et al.'s review [22,23].

In the present study, we demonstrated that AT normalized salivary cortisol levels; the levels were higher in the morning, and the postoperative slope of salivary cortisol was reversed compared with a preoperative slope. Our results suggest that a chronic stressful state due to OSA may be resolved by AT, resulting in an

Table 2
Comparison of salivary cortisol in the preoperative and postoperative groups.

Cortisol	Preoperative ($n = 13$)	Postoperative ($n = 13$)	*P*-value
n-sCor	0.05 ± 0.03	0.03 ± 0.03	0.121
m-sCor	0.22 ± 0.15	0.37 ± 0.21	0.031
sub-sCor	0.17 ± 0.16	0.34 ± 0.19	0.013
r-sCor	6.20 ± 5.57	17.67 ± 12.75	0.009

n-sCor, level of salivary cortisol before PSG; m-sCor, level of salivary cortisol after PSG; sub-sCor, subtraction of the level of salivary cortisol before PSG from the level of salivary cortisol after PSG; r-sCor, ratio of the level of salivary cortisol after PSG to the level of salivary cortisol before PSG.

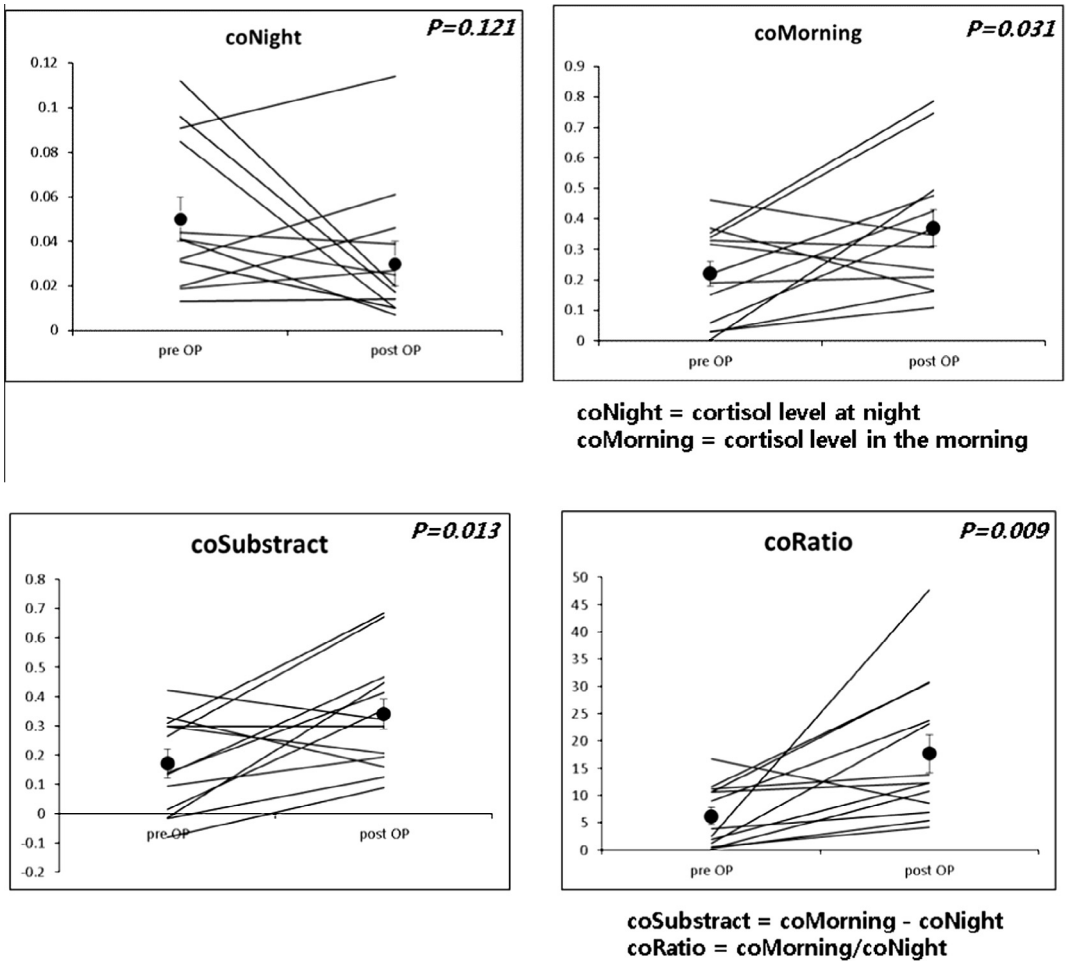

Fig. 1. The change of salivary cortisol parameters between the pre-operative and post-operative groups (3 months later after the AT).

elevation of the peak cortisol level in the morning, in contrast to the hypothesis of Buckley and Schatzberg [18].

The most common cause of pediatric OSAS is adenotonsillar hypertrophy, and so the treatment of choice for pediatric OSA is usually AT. Several reports have indicated that AT may improve neurobehavioral complications and cardiovascular problems [1,2]. Ali et al. [24] demonstrated that, after AT, the OSAS group had a significant reduction in aggression, inattention, and hyperactivity and an improvement in vigilance. They concluded that the improved behavior and functioning were associated with resolution of mild to moderate OSAS. A meta-analysis by Brietzke and Gallagher [25] showed that normalization of PSG parameters occurred in 82.9% of otherwise healthy children who underwent AT.

However, a multi-center, single-blind, randomized, controlled trial by Marcus et al. [26] demonstrated that surgical treatment for OSAS in school-age children did not significantly improve attention or executive function, as measured by neuropsychological testing, but did reduce symptoms and improve secondary outcomes of behavior, quality of life, and polysomnographic findings compared with a strategy of watchful waiting.

In our study, though KOSA-18 scores were improved significantly after AT, KMPESS scores did not show a significant change with AT. The Korean version of OSA-18 has reported validity and utility for assessing sleep quality [16]. Thus, the KOSA-18 score could reflect improved sleep status after AT. However, the KMPESS result may be explained by previous studies showing that excessive daytime sleepiness is seen less frequently as a presenting complaint in children with SDB, in contrast to adults.

When all of the above is taken into consideration, though PSG is the best way to diagnose OSAS preoperatively and evaluate the postoperative state, it nevertheless cannot be applied to all pre- and postoperative cases.

At this point, measuring salivary cortisol in children is practical because it is a safe, easy, non-invasive, and time-saving method, especially in children.

To our knowledge, this is first study to examine changes in salivary cortisol levels after AT in pediatric OSA patients.

However, it should be noted that this study has some limitations. First, it was not possible to use a control group of children who were diagnosed with OSAS and who did not undergo AT but did undergo repeated salivary cortisol measurements. Thus, we cannot exclude the possibility that the improvement may be due to growth of the airway, regression of lymphoid tissue, or routine medical care. Second, even though the HPA axis shows diurnal variation, we performed sampling at only two time-points.

However, considering the previous report showing a diurnal rhythm for salivary alpha-amylase, calculation of the diurnal slope with these measurements may be an alternative analysis strategy for assessing altered diurnal rhythm [27].

Moreover, according to Out et al. [28], the two time-point sampling, in the morning (on waking) and in the evening, was sufficient to accurately characterize the diurnal slope. Third, the follow-up period of only three months may not have been long enough to show the full response to surgery. Fourth, subgrouping of OSAS patients according to AHI was not performed due to the inadequate number of patients enrolled.

5. Conclusions

This study suggests that AT, as a treatment of choice for pediatric OSAS, can normalize disturbed cortisol secretion in pediatric OSAS patients, which may also indicate normalization of the disturbed HPA axis. Assessment of salivary cortisol in children with OSAS may be a useful tool for postoperative management planning and follow-up.

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Conflict of interest

The ICMJE Uniform Disclosure Form for Potential Conflicts of Interest associated with this article can be viewed by clicking on the following link: http://dx.doi.org/10.1016/j.sleep.2013.12.019.

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